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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/886,241	06/21/2001	Susana Salceda	DEX-0209	5811

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EXAMINER
HARRIS, ALANA M

ART UNIT	PAPER NUMBER
1642	9

DATE MAILED: 01/28/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/886,241	SALCEDA ET AL.	
	Examiner	Art Unit	
	Alana M. Harris, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

P riod for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2002* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-15* is/are pending in the application.

4a) Of the above claim(s) *1,2 and 8-15* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-7* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *7* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of Group XIV in Paper No. 8, received October 30, 2002 is acknowledged. The traversal is on the ground(s) that "[a] proper search of the prior art relating to any of the polynucleotides sequences as set for in Groups I-V, should...reveal art relating to polypeptides encoded...". Furthermore, Applicants set forth the criteria listed in MPEP 803 providing that inventions be independent or distinct and that there would be a serious burden on the Examiner if the restriction is not required. This is not found persuasive because a search of SEQ ID NO: 4 would not be a search of SEQ ID NO: 3 or 5, for example. At the most these three sequences share just 47% sequence homology as seen in the accompanying sequence alignment and share no common core structure.

The requirement is still deemed proper and is therefore made FINAL.

2. Claims 1-15 are pending.

Claims 1, 2 and 8-15, drawn to non-elected inventions are not examined on the merits.

Claims 3-7 are examined on the merits.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the

art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

4. Claims 3-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The written description in this case only sets forth a BSG as SEQ ID NO: 4 and not variants, analogs or derivatives of SEQ ID NO: 4, which are to be implemented in Applicants' methods.

Vas-Cath Inc. V. Mahurkar, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116). Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 USC 112 is severable from its enablement provision (see page 115).

Applicants are not required to disclose every species encompassed by a genus. For example as indicated in *The Regents of the University of California v. Eli Lilly* (43 USPQ2d 1398-1412),, the description of a genus is achieved by the recitation of a representative number of DNA molecules, usually defined by a nucleotide sequence, falling within the scope of the claimed genus. At section B(1), the court states that "An adequate written description of a DNA...'requires a precise definition, such as by

structure, formula, chemical name, or physical properties', not a mere wish or plan for obtaining the claimed chemical invention".

Applicants broadly claim methods of diagnosing the presence, metastases of breast cancer in a patient, as well as staging and monitoring a change in stage of breast cancer in a patient evaluating the levels of BSG. However, Applicant is not entitled, nor is the specification enabled for the use of all variants, analogs and derivatives of the BSG identified as SEQ ID NO: 4 which may or may not be effective as a breast cancer marker. Applicant is not permitted to claim all polynucleotides that are encompassed by the claims, hence not entitled to the wide breadth of the claims at issue. No disclosure of any other (examined) BSG, SEQ ID NO: 4-derived polynucleotides, beyond the mention of SEQ ID NO: 4 is made in the specification. The recitation "BSG" in Applicant's claims encompasses BSG variants. There is no description of what sites within the polynucleotide sequence of SEQ ID NO: 4 at which variability may be tolerated and no information regarding the relation of the encoded protein's structure to function. Structural features that could distinguish the compounds in the genus from others excluded are missing from the disclosure.

This is insufficient to support the generic claims as provided by the Interim Written Description Guidelines published in the June 15, 1998 Federal Register at Volume 63, Number 114, pages 32639-32645.

5. Claims 3-7 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable

one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 3-7 are broadly drawn to methods of determining comparative levels of BSG between individuals with and without breast cancer. The methods also encompass the use of variants of SEQ ID NO: 4, see page 15, lines 29-31 in order to assess whether or not the patient definitively has breast cancer, as well as monitoring and staging the cancer. The diagnostic methods include polymerase chain reaction (PCR), as well as semi-quantitative polymerase chain reaction (SQ-PCR), see page 80.

Applicants have termed the target polynucleotide, BSG. As disclosed in the specification BSG is a term used for breast specific polynucleotides and polypeptides, see page 1, lines 17-20. BSG also refers to the native protein expressed by the gene comprising the polynucleotide sequence of SEQ ID NO: 4, see page 3, lines 12-19. Furthermore, SEQ ID NO: 4 is identified as sqmam042, se page 86, lines 33-38.

The specification asserts that sqmam042 was expressed in all tissues of Table 7 found on page 86, except for normal liver. This result is not indicative of breast cancer. The specification does not enable one of ordinary skill in the art to definitively assess the incidence of any type of cancer, particularly breast cancer in a test sample. The evidence presented in the specification does point to the high occurrence of sqmam042/SEQ ID NO: 4 in breast tissues, but this is not sufficient in implementing the said sequence in a molecular based diagnostic method for breast cancer, see Table 8, page 87. Furthermore, Applicants have not provided any disclosure enabling the use of variant sequences of SEQ ID NO: 4. There is no disclosure designating what changes

to the sequences could be tolerated enabling one of ordinary skill in the art to make and use the said sequences in any diagnostic method. The experimental design presented in the specification lacks information regarding the applicability of SEQ ID NO: 4 and variant sequences thereof in diagnostic methods relative to breast diseases. Furthermore, given that four out of six matching mammary gland samples did not show differential expression between normal and cancer samples it is not reasonable to conclude that SEQ ID NO: 4 and its variant sequences would be effective in yielding a discriminate diagnosis, see page 88, lines 3-8.

Applicants have not set forth any supporting evidence that suggests that SEQ ID NO: 4 is a unique tumor or molecular marker for breast cancer. In addition, Tockman et al. (Cancer Research 52:2711s-2718s, 1992) teach considerations necessary for a suspected cancer biomarker (intermediate end point marker) to have efficacy and success in a clinical application. Although the reference is drawn to biomarkers for early lung cancer detection, the basic principles taught are clearly applicable to other oncogenic disorders. Tockman teaches that prior to the successful application of newly described markers, research must validate the markers against acknowledged disease end points, establish quantitative criteria for marker presence/absence and confirm marker predictive value in prospective population trials, see abstract. Early stage markers of carcinogenesis have clear biological plausibility as markers of preclinical cancer and **if validated** (emphasis added) can be used for population screening (p. 2713s, column 1). The reference further teaches that once selected, the sensitivity and specificity of the biomarker must be validated to a known (histology/cytology-confirmed)

cancer outcome. The essential element of the validation of an early detection marker is the ability to test the marker on clinical material obtained from subjects monitored in advance of clinical cancer and *link* those marker results with subsequent histological confirmation of disease. "This irrefutable link between antecedent marker and subsequent acknowledged disease is the essence of a valid intermediate end point [marker]", see page 2714s, column 1, Biomarker Validation against Acknowledged Disease End Points section. Clearly, prior to the successful application of newly described markers, markers must be validated against acknowledged disease end points and the marker predictive value must be confirmed in prospective population trials, see page 2716s, column 2, Summary section. Tockman reiterates that the predictability of the art in regards to cancer prognosis and the estimation of life expectancies within a population with a disease or disorder is highly speculative and unpredictable.

Based on the analysis set forth it would require undue experimentation for the skilled artisan to practice this invention because there is no support in the specification for the enablement of the broadly claimed invention. Therefore, in view of the insufficient guidance in the specification, extensive experimentation would be required to enable the claims.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 3-7 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a. Claims 3-7 are vague and indefinite in the recitation "BSG". BSG is not an art recognized term solely attributed to breast cancer. The term could be an acronym for the British Society of Gastroenterology or brain stem glioma. Applicants could obviate this instant rejection by listing the meaning or full terminology before the acronym in the initial citing of the first examined claim in which it appears.

Claim Rejections - 35 USC § 101

8. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

9. Claims 3-7 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial, credible or asserted asserted utility or a well established utility.

Claims 3-7 are broadly drawn to methods of detecting a target polynucleotide within a test sample utilizing a polynucleotide, SEQ ID NO: 4 and variant sequences of SEQ ID NO: 4 in order to assess whether or not the test sample contains a polynucleotide indicative of breast cancer. These diagnostic methods include for example PCR and SQ-PCR. The specification also contemplates the use of these methods for diagnosing, staging, monitoring breast cancer. Applicants have disclosed in the specification that the examined BSG, SEQ ID NO: 4 is also termed sqmam042.

Sqmam04 was expressed in breast tissues, but did not show differential expression between normal and cancer mammary gland samples, see page 88, lines 3-8. This result does not support Applicants' asserted use of the claimed methods for detection of breast cancer. There is no disclosure or working examples that demonstrate the specifically asserted utility and evidences a substantial utility was well established at the time of filing. Applicants have provided information that simply supports the fact that SEQ ID NO: 4/sqmam042 may be expressed especially in breast tissues, however that is not regarded as definitive, Table 7, page 87. There is no information supporting the use of SEQ ID NO: 4/sqmam042 as a specific tumor marker to be implemented in the broadly claimed methods. The specification does not exemplify the use of any of the said sequences in differential expression in normal breast tissue versus high risk (potentially diseased) breast tissue or its reliability as biomarkers, which may signal a stage of carcinogenesis. Based on the analysis set forth above the specification does not exemplify sufficient findings that constitute a specific, substantial or credible utility.

Claims 3-7 also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific, substantial or credible asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

10. Claims 3-7 are free of the art.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (703) 306-5880. The examiner can normally be reached on 6:30 am to 4:00 pm, with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa, Ph.D. can be reached on (703) 308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4315 for regular communications and (703) 308-4315 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703)308-0196.

ALANA HARRIS
PATENT EXAMINER

Alana M. Harris, Ph.D.
January 27, 2003